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10/522,371	01/25/2005	William Richard Cross	15892.9	1386

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,371	CROSS ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-26 and 29-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-26 and 29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/04/2008 has been entered.

Claims 13, 17-19, 24, 31, 32 have been amended, claims 33 and 34 have been newly added and claims 27 and 28 have been newly canceled.

Claims 13-26, 29-34 are currently pending and have been examined on the merits.

Response to Arguments

Applicant's arguments filed 11/04/2008 have been fully considered but they are not persuasive. The arguments have been addressed in so far as they relate to the new rejections.

Applicant argues that the Zhang reference does not teach each and every element of the claimed invention. Applicant asserts that Zhang is completely devoid of teaching a method of production of stratified, terminally-differentiated mammalian urothelium in which urothelial cells, isolated from the mammalian body, are passaged

through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum to form the urothelium as recited in claim 13.

This is not found persuasive because the method taught by Zhang et al. inherently contains all the claim limitations. To invalidate a patent by anticipation, a prior art reference normally needs to disclose each and every limitation of the claim. See *Standard Havens Prods., Inc. v. Gencor Indus., Inc.*, 953 F.2d 1360, 1369, 21 USPQ2d 1321, 1328 (Fed. Cir. 1991). However, a prior art reference may anticipate when the claim limitation or limitations not expressly found in that reference are nonetheless inherent in it. See *id.* and *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 630, 2 USPQ2d 1051,1053 (Fed. Cir. 1987). Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates. See *In re King*, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). **Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art.** See *Titanium Metals*, 778 F.2d at 780. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. See *id.* at 782. However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. See *id.* at 782 ("Congress has not seen fit to permit the patenting of an old [composition], known to others…, by one who has discovered its…useful properties."); *Verdegaal Bros.*, 814 F.2d at 633.

This court's decision in *Titanium Metals* illustrates these principles. See *Titanium Metals*, 778 F.2d at 775. In *Titanium Metals*, the patent applicants sought a patent for a titanium alloy containing various ranges of nickel, molybdenum, iron, and titanium. The claims also required that the alloy be "characterized by good corrosion resistance in hot brine environments." *Titanium Metals*, 778 F.2d at 776. A prior art reference disclosed a titanium alloy falling within the claimed ranges, but did not disclose any corrosion-resistant properties. This court affirmed a decision of the PTO Board of Appeals finding the claimed invention unpatentable as anticipated. This court concluded that the claimed alloy was not novel, noting, "it is immaterial, on the issue of their novelty, what inherent properties the alloys have or whether these applicants discovered certain inherent properties." *Id*. at 782. This same reasoning holds true when it is not a property, but an ingredient, which is inherently contained in the prior art. The public remains free to make, use, or sell prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate. The doctrine of anticipation by inherency, among other doctrines, enforces that basic principle." See *Atlas Powder Co. v. IRECO Inc.*, 51 USPQ2d 1943 (Fed. Cir. 1999).

Thus, a reference may be anticipatory if it discloses every limitation of the claimed invention either explicitly or inherently. A reference includes an inherent characteristic if that characteristic is the natural result flowing from the reference's explicitly explicated limitations. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

Zhang et al. teach the establishment and expansion of cultures of rat (mammalian) urothelial cells in KSFM that contains serum (page 419, materials and methods). The passaging of cells, as taught by Zhang et al., inherently requires that the cells are trypsinized and redispersed into a second medium that also contains serum (page 422, column 2). In addition, the KSFM-CM media used was prepared to contain FBS as well (page 422, column 1, 3rd full paragraph and table 1, media 6). Since Zhang et al. teach a method that includes all the method steps as claimed by Applicant, Zhang et al. inherently anticipates the claimed invention.

Applicant argues that Zhang teaches that when RUC cells were placed into standard medium containing serum, the cells showed low plating efficiency, poor growth characteristics, a limited potential for cell division and failed to differentiate in vitro. Applicant asserts that this teaches away from the presently claimed invention.

This is not found persuasive because Zhang goes on to state that there are additional types of media beyond the standard medium (specifically CM-KSFM) that allow for an RUCs to be cultured for up to 18 passages (page 428, first paragraph). Zhang is clearly indicating that a more sophisticated medium than the standard medium is required for the achievement of an optimal engineered urothelial sheet. Applicant's claimed method steps correspond to routine passaging of cells (i.e. trypsinizing the cultures which requires disaggregating the cells and re-seeding them with new media which requires dispersing the cells) that are practiced by cell culture laboratories to expand cultures.

Applicant argues that the Liebert reference is completely devoid of teaching a method of production of stratified, terminally-differentiated mammalian urothelium in which urothelial cells, isolated from the mammalian body, are passaged through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum to form the urothelium as recited in claim 13. Applicant asserts that once the urothelium cells of Liebert are cultured in a media containing serum, such cells are not dispersed into the second media containing serum. Applicant asserts that the method disclosed in Liebert does not result in the high transepithelial resistance that is characteristic of stratified, terminally-differentiated urothelium.

This is not found persuasive because all the claimed method steps of Applicant's invention (i.e. the passaging of urothelial cells using media containing serum) are explicitly disclosed in Liebert et al. (page 184 column 2, lines 22-32). If the end product is not the same, then Applicant's claimed method must be missing some required element that would ensure the same result.

Applicant argues that the Seijiro reference is completely devoid of teaching a method of production of stratified, terminally-differentiated mammalian urothelium in which urothelial cells, isolated from the mammalian body, are passaged through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum to form the urothelium as recited in claim 13.

This is not found persuasive because the Seijiro reference is cited as a secondary reference to demonstrate the suitability of adult bovine serum for the culture

of animal cells. The primary references of Zhang and Liebert are interpreted to teach the method of claim 13 as described above.

Applicant argues that the Judd reference is completely devoid of teaching a method of production of stratified, terminally-differentiated mammalian urothelium in which urothelial cells, isolated from the mammalian body, are passaged through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum to form the urothelium as recited in claim 13. Applicant asserts that Judd does not teach the use of a defined medium for cell differentiation and a skilled artisan would not consult Judd in preparing a cell culture media that promotes cell differentiation.

This is not found persuasive because the Judd reference is cited as a secondary reference and indicates that MCDB-153 is a suitable alternative for KSFM medium in a defined system for epithelial cell culture (column 5 lines 1-13). That is as a primary media for the use of culturing epithelial cells, MCDB-153 and KSFM are considered to be art recognized equivalents. The primary references of Zhang and Liebert are interpreted to teach the method of claim 13 as described above requiring the teaching of Judd for the reasonable expectation of success in substituting one well known media for another.

Applicant argues that nothing in Cross teaches that urothelium cells grown in a serum containing media are redispersed into another serum-containing media.

This is not found persuasive because while Cross is silent with regard to the exact culture steps used to expand the urothelial cells, Zhang provides the method

steps known in the art which include passaging the cells with serum-containing media. Passaging of cells , as described above, requires the dispersing of cells from one media to another media.

Applicant argues that the art of record teach away from the presently claimed invention. Applicant asserts that none of the cited references recite the claimed method steps. Applicant asserts that none of the art of record teaches a redispersal from a serum-containing medium into another serum-containing medium.

This is not found persuasive because Applicant is not taking into consideration that the steps for passaging of the cells cited in the prior art inherently include these exact method steps. Freshney (Culture of Animal Cells, page 1, 1994) teaches the well known steps of passaging of adherent cell lines (otherwise known as subculture) as evidence of this inherency.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-26, 29-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-26, 29-34 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Zhang et al. recites the same steps as claimed by Applicant, (establishing a primary culture with serum free media and expanding the cells in serum containing media for subsequent passages without a feeder layer or exposure to 3T3 cells), yet does not describe the exact same results (page 427 column 1). It appears that Applicant's claimed method must be missing an essential method step or component that ensures a stratified, terminally-differentiated urothelium as the end result of the method. This is further supported by the Southgate reference (IDS reference #7) wherein certain factors and components are taught to greatly affect the final outcome of an urothelial culture (page 586, column 1, 1st paragraph- 2nd paragraph and page 590, column 2, 2nd paragraph). Applicant's claimed method steps correspond to routine passaging of cells (i.e. trypsinizing the cultures and re-seeding them with new media) that is practiced by many labs to expand cultures. Since Applicant is claiming that the end result of Applicant's method is different, it would appear that some required element must be missing to ensure the end result as claimed. All the essential method steps and media components required for the end result of a stratified, differentiated urothelium must be included in the claimed method in order to be complete. This includes the essential media components (such as growth factors or other additives) as well as the length of culture time required for the production of a stratified, terminally-differentiated urothelium.

Claims 17 and 18 recite the limitation “the concentration of the components of the serum” in line 2. This is indefinite as it is unclear which components of the serum have the claimed concentration as well as insufficient antecedent basis for this limitation in the claim.

Claim 34 recites the limitation "the third culture medium" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim as none of the preceding steps include adding a third culture medium.

In addition, the term "low calcium cell culture medium" in claim 34 is a relative term which renders the claim indefinite. The term "low calcium" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear from Applicant’s specification and from the prior art where the cut-off amount of calcium is for low calcium culture medium thus rendering the metes and bounds of the claim unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13, 15, 17-19, 21, 23-26, 29-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (In Vitro Cell. Dev. Biol.-Animal 2001).

Amended claim 13 is now drawn to a method of production of stratified, terminally-differentiated mammalian urothelium in which urothelial cells, isolated from the mammalian body, are passaged through a first nutrient medium containing serum and then redispersed before being added to a second medium containing serum to form the urothelium.

Claim 15 includes wherein the serum is bovine serum.

Claims 17-19 include the concentration range of the components of the serum.

Claim 21 includes wherein the nutrient medium is KSFM.

Claim 23 is drawn to the urothelium produced by the method of claim 13.

Amended claim 24 is drawn to a method of production of stratified, differentiated mammalian urothelium comprising: disaggregating cells of a primary culture of mammalian urothelial cells; dispersing the cells of the primary culture into a first differentiation medium that includes whole serum; culturing the cells to form a secondary culture having aggregated cells, dispersing and disaggregating the cells into a second differentiation medium that includes whole serum; and culturing the cells so as to form stratified, terminally-differentiated mammalian urothelium.

Claims 25 and 26 include wherein the aggregated cells are at least partially confluent and approach confluency respectively.

Claims 29 and 30 include wherein the serum is between about 1% and 30% and 4% and 6% of the medium respectively.

Amended claim 31 includes wherein the first, second differentiation culture medium is one of MCDB-153, KSFM, or derived thereof.

Amended claim 32 includes wherein the first, second differentiation culture medium is supplemented by EGF, BPE, or CT.

New claim 33 is drawn to the method of claim 24 and further includes increasing the calcium concentration in the second differentiation cell culture medium.

This is interpreted as requiring that the calcium concentration be increased compared to any prior media used.

New claim 34 is drawn to a method of production of stratified, differentiated mammalian urothelium, the method comprising disaggregating and dispersing primary cells into a first differentiation low calcium medium that includes at least 5% whole serum, culturing to form a secondary culture; dispersing and disaggregating the cells into a second differentiation low calcium culture medium that includes at least 5% whole serum and culturing the cells with medium with increasing calcium concentration to form the stratified, terminally-differentiated urothelium.

This is interpreted as requiring that the differentiation media used after the first and second differentiation media have an increased calcium concentration compared to any prior media used.

Aggregated cells are interpreted to mean at least two or more cells that are touching each other.

The terms “first” and “second” with regard to the medium are NOT interpreted as requiring different mediums for these steps or that additional steps of adding medium prior to the differentiation medium are excluded. The claims are deemed to be open-ended, allowing for other method steps such as the seeding of primary cultures with serum-free media prior to the passaging with serum-containing media.

Zhang teaches a method for expansion and long-term culture of differentiated normal rat urothelium cells in vitro wherein the urothelium cells are isolated from the mammalian body (page 419 materials and methods) and cultured with a media that contains KSFM and conditioned medium (CM) with 5% fetal bovine serum (FBS) (page 422 table 1, media number 6). Detailed investigations of culture conditions showed that CM-KSFM yielded a differentiated, multilayered (stratified) structure (abstract). Establishment of primary cultures with a serum free media that contains EGF, BPE and CT and has a calcium concentration of 0.09 mM is taught (page 419 materials and methods) along with subsequent expansion with different medias containing whole serum (one with 5% FBS) until passage 2, which would inherently require a second and third culture medium that includes whole serum (page 422, column 1, paragraph 3-4). The amount of calcium used in the passaging steps is taught to be 2.5 mM (fig. 4 page 422) and is interpreted as increasing the calcium concentration of the differentiation medium from the initial medium used for the primary cultures. The cells are at least partially confluent and approaching confluency and therefore contain cells that are

touching each other (aggregated)(page 427 column 1). Though the final product of the method is not described as stratified and terminally-differentiated (page 427), the final product is deemed to be the same as that produced by the claimed method since all the claimed method steps are carried out.

Since Zhang et al. is explicitly carrying out all the method steps as claimed by Applicant, Applicant's method as claimed is anticipated.

Claims 13 and 15, 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Liebert et al (Differentiation 1997).

Liebert teaches a method of producing a stratified urothelium using urothelial cells that were passaged with media containing bovine serum (page 184 column 2 lines 22-32). Passaging involves the disaggregating and dispersal of cells from one media to another media and therefore the method steps as claimed by Applicant are included.

Therefore, Liebert anticipates Applicant's invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (In Vitro Cell. Dev. Biol.-Animal 2001) or Liebert et al (Differentiation 1997) as applied to claims 13 and 15 above and further in view of Seijiro et al (US 4,654,304).

Claim 16 is drawn to the method of claim 15 wherein the serum is adult bovine serum.

Zhang or Liebert teach the method of claim 15 as described above, but do not include adult bovine specifically.

Seijiro teaches that serum to be used in the cultivation of animal cells or tissues may be derived from any species, although bovine, among others, may be advantageously used for reasons of their ready availability (column 1 lines 64-68). The mammals from which the serum is derived may be at any age, e.g., fetuses, newborns,

youngs or adults (column 2 lines 1-2). Clearly adult bovine serum is considered by Seijiro to be a suitable substitute for fetal or newborn bovine serum.

Therefore, one of ordinary skill in the art would have been motivated to substitute adult bovine serum for fetal or newborn bovine serum because Seijiro teaches that mammals from which the serum is derived may be at any age, e.g., fetuses, newborns, youngs or adults (column 2 lines 1-2). One of ordinary skill in the art would have had a reasonable expectation of success because Seijiro had demonstrated that the adult bovine serum possessed growth promoting substances (column 11 table 4).

Therefore, the combined teachings of Seijiro with any one of Zhang, Liebert or Scriven render obvious the invention as claimed.

Claims 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (In Vitro Cell. Dev. Biol.-Animal 2001) as applied to claim 13 above and further in view of Judd et al (US 6,692,961 B1).

Claim 20 includes wherein the nutrient medium is, or is a derivative of, MCDB-153 medium.

Claim 22 includes wherein the nutrient medium is supplemented by one or more of EGF, BPE, or CT.

Zhang teaches the method of claim 13 using KSFM, but does not teach the use of MCDB-153 medium.

Judd teaches a defined system for epithelial cell culture and indicates that MCDB-153 (which includes EGF and BPE) is a suitable alternative for KSFM medium

(column 5 lines 1-13). Judd also teaches the benefits of adding EGF and/or cholera toxin (CT) to the media as well (column 11 lines 10-40).

Therefore, one of ordinary skill in the art would have been motivated to substitute MCDB-153 medium for KSFM in the method of Zhang because Judd indicates that MCDB-153 is a suitable alternative for KSFM medium (column 5 lines 1-13). One of ordinary skill in the art would have had a reasonable expectation of success because the teachings of Judd were drawn to the in vitro cultivation of animal epithelial cells.

Therefore, the combined teachings of Zhang and Judd render obvious the invention as claimed.

Claims 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liebert et al (Differentiation 1997) as applied to claims 13 and 15, 23 above and further in view of Judd et al (US 6,692,961 B1).

Liebert teaches the method of claim 13 as described above, but does not teach the use of MCDB-153 medium or supplementing with EGF, BPE, CT.

Judd teaches a defined system for epithelial cell culture and indicates that MCDB-153 (which includes EGF and BPE) is a suitable alternative for KSFM medium (column 5 lines 1-13). Judd also teaches the benefits of adding EGF and/or cholera toxin (CT) to the media as well (column 11 lines 10-40).

Therefore, one of ordinary skill in the art would have been motivated to use MCDB-153 in the method of Liebert because Judd teaches that MCDB-153 is a suitable

alternative for the media that Liebert uses (KSFM). One of ordinary skill in the art would have been motivated to add EGF or CT to the culture media of Liebert because Judd teaches that these agents are beneficial in the growth of epithelial cells. One of ordinary skill in the art would have had a reasonable expectation of success because both Judd and Liebert are growing epithelial cell cultures.

Therefore, the combined teachings of Liebert and Judd render obvious the invention as claimed.

Claims 13-15, 17-19, 21, 23-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cross et al. (Biochemical Society Transactions 2001, from IDS) in view of Zhang et al (In Vitro Cell. Dev. Biol.-Animal 2001).

Cross et al. teach that normal human urothelial cells propagated in serum-free medium exhibited a low transepithelial electrical resistance and a high FITC-Dextran permeability. The addition of serum to the culture system resulted in urothelial stratification, intercellular tight junction formation, a high transepithelial electrical resistance, a low FITC-Dextran permeability and the expression of amiloride sensitive sodium channels. This human *in vitro* urothelial tissue model expresses many of the morphological and functional properties of the *in vivo* system (abstract).

Cross et al. are silent with regard to the exact media used and the number of cell passages from the establishment of primary cultures to the final product.

Zhang et al. teach that KSFM provides an optimal medium to separate urothelial cells selectively from other types of cells and can be used for an initial culture before subculturing (redispersing) the cells in a serum-supplemented media for long-term cultures (page 428, column 1, paragraph 3). Establishment of primary cultures with a serum free media that contains EGF, BPE and CT is taught (page 419 materials and methods) along with subsequent expansion with different medias containing serum (one with 5% FBS) until passage 2, which would inherently require a second and third culture medium that includes serum (page 422, column 1, paragraph 3-4). The cells are at least partially confluent and approaching confluency and therefore contain cells that are touching each other (aggregated) (page 427 column 1).

Therefore, one of ordinary skill in the art would have been motivated to use a serum free media such as KSFM in the establishment of primary urothelial cultures because Zhang et al. teach that KSFM provides an optimal medium to separate urothelial cells selectively from other types of cells and can be used for an initial culture before subculturing (redispersing) the cells. One of ordinary skill in the art would have been motivated to switch to media containing serum for the subsequent passages of urothelial cells because Cross et al. teach that the addition of serum containing media to urothelial cultures yields a human *in vitro* urothelial tissue model expressing many of the morphological and functional properties of the *in vivo* system (abstract). The number of passages required would have been a matter of routine optimization, the artisan of ordinary skill would be motivated to adjust the number of passages depending on the amount of urothelium required for the end product. One of ordinary skill in the art would

have been motivated to use bovine serum at about 5% and low increasing levels of calcium because Zhang et al. teach that these are suitable additions and concentrations for the growth of urothelial cells. One of ordinary skill in the art would have had a reasonable expectation of success in using these techniques in the method of Cross et al. because Zhang et al. teach that culture techniques such as these are applicable to other primary tissue culture systems where potential contamination and subsequent overgrowth with fibroblasts remain a problem (page 428, column 2, last paragraph).

Therefore, the combined teachings of Cross et al. and Zhang et al. render obvious Applicant's invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Laura Schuberg